

Psychological treatment can modulate the skin reaction to histamine in pollen allergic humans¹

Effects of mental allergy therapy – the HILDESHEIM HEALTH TRAINING®

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Key Words (Mesh)

Allergy, psychotherapy, skin prick test, mental health, mast cells, histamine release, cognition, learning, mental competency.

Summary:

Background: There is growing evidence indicating that allergy and immune function can be modified by classical conditioning techniques, stress and other psychological factors, but the neural mechanisms remain unclear.

Objective: The reported experiments examine the involvement of psychological factors on allergic immune response. Psychological intervention like mental health training called HILDESHEIM HEALTH TRAINING provides further evidence that the human organism might be able to react differentially with more or less allergic immune responses after “Feedforward-treatment” like changing internal stimuli such as cognition and emotion, self hypnotic imagination or classical conditioning of healthy reaction.

Methods: In a randomised study HILDESHEIM HEALTH TRAINING, which includes behaviour therapy, classical conditioning, hypnosis and neuro-linguistic-programming (nlp), was evaluated with psychological tests and skin prick tests as a read-out system.

Results: While the skin wheal reaction to histamine was clearly enhanced during the pollen flight season in allergic control individuals, it remained unchanged in pollen allergic individuals who received mental allergy therapy.

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Conclusion: The skin reaction of birch pollen allergic patients towards histamine provocation was modulated. This suggests that the immune response can be influenced by psychological intervention such as HILDESHEIM HEALTH TRAINING.

Psychologische Interventionen können die Hautreaktion auf eine Histaminprovokation beeinflussen

Effekte mentaler Allergiebehandlung - Evaluation des **HILDESHEIMER GESUNDHEITSTRAININGS®**

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Schlüsselworte: Allergie, Psychotherapie, Hautreaktion, Pricktest, Mentaltraining, Emotion, Kognition, Histamin.

Zusammenfassung: Es gibt zunehmend Hinweise, dass allergische Immunfunktionen durch Konditionierungstechniken, Stress oder anderen psychologischen Faktoren beeinflusst werden können. Der vorliegende Artikel zeigt, wie Feedforward-Effekte mit Hilfe multimodaler psychologischer Methoden wie das Hildesheimer GesundheitsTraining die Immunfunktion beeinflussen.

In einer randomisierten Studie wurde anhand von psychologischen Tests und Haut-Prick-Tests untersucht, wie sich eine Kombination aus Verhaltenstherapie, Hypnose, Klassischer Konditionierung und NLP auf die Immunfunktion bei Birkenpollenallergikern auswirken.

Während die Hautreaktionen auf Histaminprovokationen bei den Probanden der Kontrollgruppen während der Birkenpollenflugsaison anstiegen, blieb sie bei den Probanden der Interventionsgruppen unverändert. Das lässt vermuten, dass komplexe psychologische Interventionen wie das Hildesheimer GesundheitsTraining die Immunantwort beeinflussen können.

Introduction:

The concept, that mast cells play a key role in the initiation of acute allergic responses has been accepted. Also a lot of evidence for a psychological neurological immunological interaction has been accepted. The recognition of importance of psychological factors increased in the last 10 years in many dermatological diseases. Recent articles were able to demonstrate changes in psychological and immunological parameters under experimental stress conditions in atopic dermatitis in comparison with control groups of persons with healthy skin and support the influence of emotional factors. [Gieler et al 2001, Niemeier et al 1999, Schneider & Gieler 2001] Also skin reactions to histamine after hypnotically induced emotions of sadness, anger, and happiness showed the influence of psychological factors. [Zachariae et al. 2001]

From a behaviour therapist's viewpoint anxiety is perceived in a framework expanded to the **psychoneuroimmunological** dimension. The association between Panic Disorder and allergic (vasomotor) reactions was found to be highly significant. A functional relationship is hypothesized in terms of conditioning cognitive and vasomotor interactions during autonomic arousal. [Schmidt-Traub 1991, Schmidt-Traub & Bamler 1992, Schmidt-Traub 1995, Schmidt-Traub & Bamler]

Other findings showed correlation for interleukin-3 production with anxiety and indicate that interleukin levels may be sensitive to the presence of anxiety and stress. [Weizmann et al. 1999] This is probably very important because interleukin seems to play a key-role in differentiating T cells between Th1 or Th2.

Pavlovian conditioning provided early impetus to the rapidly expanding knowledge of bi-directional communication among the immune, endocrine, and central nervous systems. Several findings on conditioning of the immune system in animals have been published since Pawlov. The phenomenology of this response has been well

characterized. And last but not least, comparable data on human research showed a bi-directional influence between the nervous system and human immune function. [Buske-Kirschbaum et al. 1992, 1994, 1997, 1998, 2001]

“Immune response can be enhanced through activity of the central nervous system.” [Russel et al. 1984] “Results support the involvement of the central nervous system in mast cell de-granulation in allergic rhinitis in humans.” [Gauci et al. 1994]

The research team of Bienenstock showed a close association between the enteric nervous system and mast cells, and also the effect of neuro peptides such as substance P which could be investigated in *in vitro* co-cultures between mast cells and nerves. This role of mast cells in the dialogue between the immune system and the nervous system was illustrated by conditioning experiments showing the de-granulation of mast cells by a conditioning stimulus. [Blennerhasset & Bienenstock 1998, Djuric et al 1995, Marshall & Bienenstock 1994, Marshall et al 1994, 1999, McKay & Bienenstock 1994, Sanico et al 1999, 2000, Suzuki et al 1999, William et al 1995]

Acute mental stress induced different cytokine profiles in patients with atopic dermatitis (AD) as compared to healthy controls. A higher stress-induced increase of cutaneous lymphocyte-associated antigen (CLA+) cells, T helper cells expressing IL-5, and both CD4 (+) and CD8 (+) lymphocytes expressing IFN-gamma in patients with AD compared to healthy controls might indicate **psychoneuro-endocrinologic** mechanisms. [Schmitt-Ott et al 1998, 2001]

However the connection between psychological and neural mechanisms remains unclear. Similarly, the way to use psychological treatment to induce neural mechanisms with biological relevance needs to be investigated.

A mental health training, called HILDESHEIM HEALTH TRAINING (HHT) was therefore developed and tested. Patients allergic to birch pollen received HILDESHEIM HEALTH TRAINING to learn how to modulate a new response of there immune system. HILDESHEIM HEALTH TRAINING uses a combination of behaviour therapy, nlp, classical conditioning and hypnosis.

The intervention was tested with reference to psychological items, medicine consumption, ailments and skin-prick-tests. Analysis is made of skin prick tests using histamine provocation measured as a standard technique in the study of allergies. A functional relationship is hypothesized in terms of psychological and somatic interactions.

Patients and Methods:

Patients: Patients allergic to birch pollen for at least 3 years (n = 72; aging from 18 to 66 years, ξ [W] [W] [W] 42 years, median: 41 years) were divided into two experimental groups (n = 41) and two control groups (n = 31). Inclusion criteria were suffering on allergic immune response on birch pollen which was IgE tested and showed in cutaneous prick testing (see table 1).

- insert table 1 here -

Psychological Intervention: The two experimental groups received the HILDESHEIM HEALTH TRAINING for the mental handling of allergies. The treatment is a group setting, which takes 8 meetings (2/week) about 2 hours working with individual conditioning, psychosocial factors and believe systems + 25 minutes relaxation. The relaxation includes hypnotically healing imagination.

The Hildesheim Health Training helps participants to find out there own experience of a healthy perception of the environment and to establish it as a feed forward regulation. One of the two experimental groups received an additional intervention (40 minutes) for building a healthy immune response (classical conditioning of a healthy immune reaction by hypnotically induced imagination, NLP). One control group (cassette) received a relaxation cassette, in order to be able to check placebo effects. It was suggested to these persons that the cassette contained highly effective healing materials. The individuals of the other control group did not receive any treatment and were requested, to behave as usual. All participants of the study were instructed to document medicine consumption and ailments in daily diary entries for the duration of the intervention. The study was single blind, with objective data acquisition (randomised). All data were from 1998 before (= t 0), during (= t 1) and after the flight season of birch pollen (= t 3).

Skin Prick Test: In all participants of the study cutaneous prick testing was performed 3-5 weeks before treatment and before the start of the birch pollen season; after intervention at the beginning of the birch pollen season; and 14 weeks later when the birch pollen season had finished.

Provocation with saline solution (NaCl 0.9%) served as a negative control to exclude non-specific irritations. A histamine provocation (Histamine: 0,01%, Allergopharma J. Ganzer KG, Reinbek, Germany) was implemented as a positive control, to exclude the risk of falsely negative results due to medication. Exclusion criteria were any non-specific irritation and any antihistamine medication or negative control on histamine. This provocation was also necessary in order to calculate the histamine equivalent of skin sensitivity in relation to skin reaction. Birch pollen extract (Allergopharma, Reinbek, Germany; 5000 BU/ml) was applied on both forearms at the following dilutions: 1:1, 1:3, 1:10, 1:30, 1:100.

The prick test was read after 15 minutes by drawing the outline of the wheals on a transparent foil, scanned (Resolution: 300dpi, range: x 0,085mm y 0,085mm) and measured as wheal area in mm² by AnalySis (Version 2.11; Softimaging Software GmbH). All statistics were calculated using the SPSS 6.0 program.

The reaction on birch pollen was calculated by histamine equivalent. According to the Nordic Guidelines the histamine equivalent is used by pharmaceutical companies to standardize the quality of allergen extracts. It is a dose-response relationship of the allergen, estimated by regression line analysis using the geometric mean of the four wheal areas obtained with each concentration, in a double-logarithmic system [Nordic Council on Medicines 1989]. The reaction on histamine was calculated as mean value of the flare size obtained on the two forearms.

It was checked that the intervalscaled data in the population were normally distributed (Kolmogorov-Smirnov-Test) and that variance homogeneity (Bartlett-Test) allowed variance analysis. A repeated-measures (within-subjects and time) analysis of variance

was calculated to check wheal differences and the development over time between the groups.

Results:

There was not any significant effect of the HILDESHEIM HEALTH TRAINING to be observed on the birch pollen extract, which was calculated by histamine equivalent, but the following other effects were shown:

- Although at the beginning of the observation period (t0) the skin reactivity (sensitivity) to histamine did not differ significantly between the groups, a rise of histamine reaction was registered (t0 to t1 and t0 to t2). It was surprising that this clear increase in wheal area was only evident in the control groups.
- A variance analysis on basis of time and measuring repetition showed a highly significant difference in histamine-induced wheal area (significance of F: < 0,000). And this development differed significantly between the groups (significance of F: < 0,030) (Table 2, Figure 1).

- insert table 2 and figure 1 here -

The significant interactions between the groups and the developments over time suggest that the skin reactions are influenced by psychological intervention.

In the control groups: Cassette (placebo) only 5 persons out of 13 could be tested at time t2. Two had stopped participating in the study, three had not appeared for the test and three others had taken antihistamine. These respondents had to be excluded and therefore the groups were combined into an intervention group and a control group.

There were 21 people in the control group as compared with 39 in the intervention group. An analysis using the Chi-Square technique indicates that results obtained on basis of this sample can not be coincidental.

The unpublished data (psychological items, medicine consumption and ailments regarding HILDESHEIM HEALTH TRAINING) confirm the read-out in the skin prick test detailed above. All the effects on mental allergy therapy is published elsewhere (Witt 1999).

Discussion:

While the histamine reaction remained almost constant in the intervention groups, its intensity increased high significantly in the control groups. Because there was shown a significantly different development between the groups by variance analysis, it seems improbable that this effect is due to variations of base values. Without any psychoneuroendocrinological effect the individuals of the HILDESHEIM HEALTH TRAINING group should have shown a development similar to the control groups. The incidence of skin reactions should have increased to the same extent as in the control group. At time t1 the control group showed a high drop out (t1: 9=50%, t2: 2=11%) because of medication. Even the high drop out in the placebo group at time t2 (t1: 4=31%, t2: 3=23%) was very special and indicates that the intervention should be more than a placebo effect. In the beginning all participants where high motivated and believed in healing imagination. But it did not work, imagination and belief was not enough. They got the most symptoms. Some persons stopped to participate, others tried to continue hearing the imagination without any medication. But later they realised that they couldn't reach improvement without any medication. Only the participants in the intervention groups reached improvement without any medication. A Chi Square supports that the drop-out differed significantly between the intervention groups (HHT +PI t1: 0 = 0%, t2: 0=0% and HHT-Basic t1: 2= 9%, t2: 2=9%) and the control groups (see table 3).

- insert table 3 here -

It seems the reactions to the birch pollen extract, which were calculated by histamine equivalent, did not show any significant effect. They were more determined by histamine sensitivity, than by the concentration of the birch extract.

The results suggest that the psychological treatment has an unspecific stimulation on the release of mast cells and in this respect an effect on allergy sensitivity which was shown in the skin prick test to histamine.

It is probable that the sensitivity increase was prevented by the psychological treatment in participants of the intervention groups and that this reflects physiologically the positive effects of such mental allergy treatments which might affect mast cells.

These results support clinically the observations of Bienenstock and coworkers, [Blennerhassett & Bienenstock 1998, Djuric et al 1995, Marshall & Bienenstock 1994, Marshall et al 1994, 1999, McKay & Bienenstock 1994, Sanico et al 1999, 2000, Suzuki et al 1999, William et al 1995] who found that contacts between mast cells and nerve membranes, and between neuropeptides such as substance P and mast cells establish a dialog between the immune system and nervous system.

The preliminary results provide further evidence in support of psychoneuro-endocrinological interaction and the positive effect of multiple psychological intervention. Also the unpublished data support existing theories [Witt 1998] , that an adjuvant psychological treatment appears to be able to reduce physiological effects, decrease medication, and can be used to eliminate side effects, support well being and be helpful in combination with hypersensitivity.

In conclusion, allergic immune processes might be influenced over complex mental procedures like HILDESHEIM HEALTH TRAINING.

Legends:

Table 1: Patients, groups and drop-out

Table 2: Skin reaction after histamine provocation

Table 3: Chi-Square

Figure 1: Development over the time

Table 1:

Patients, groups and drop-out				
	Intervention Groups		Control Groups	
	HHT- Basis+ PI	HHT-Basis	Cassette (Placebo)	No Treatment
t ₀ (before HHT)	18	23	13	18
t ₁ (after tHHT)	17	22	9	9
t ₂ (follow-up 14 weeks after HHT)	17	22	5	16
Drop-out	2		10	

HHT = Hildesheimer Health Training

Table 2:

Skin Reaction after histamine provocation						
Analysis of variance [wheal area F < 0,000] [development between groups F < 0,030]						
	intervention group (HHT-Groups)			control group		
	\bar{w} ξ	s	n	\bar{w} ξ	s	n
T ₀ (before HHT)	825	393	41	706	516	31
T ₁ (after HHT)	896	375	39	922	493	18
T ₂ (follow-up 14 weeks after HHT)	906	445	39	1067	515	21

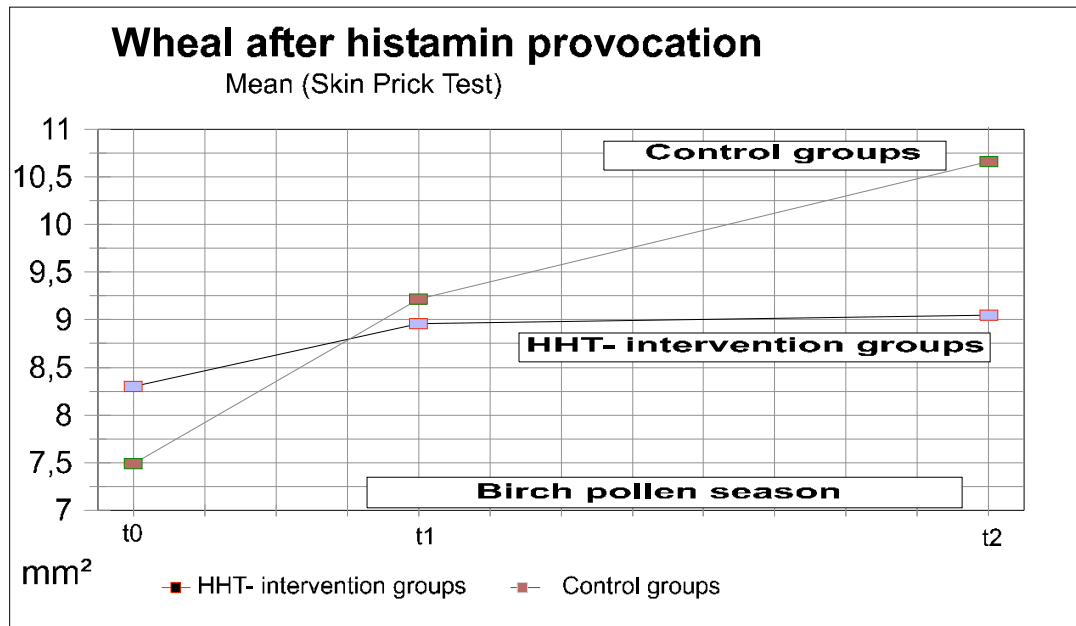
Minimum 0,29 mm², Maximum 24,0 mm²

HHT = Hildesheimer Health Training

Table 3:

Chi-Square	Pearson	Intervention group		Control group	
		tested	drop-outs	tested	drop-outs
<i>t1 (before HHT)</i>	P < 0,000	39	2	18	13
<i>t2 (after HHT)</i>	P < 0,002	39	2	21	10

Figure 1: Development over the time



Intervention group	t0 n = 41	t1 n = 39	t2 n = 39
Control group	t0 n = 31	t1 n = 18	t2 n = 21

HHT = Hildesheimer Health Training

Quotation by variance analysis: While the histamine reaction remained almost constant in the intervention group, its intensity increased high significant in the control group. There was shown a significantly different development between the groups.

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